TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
P66806US0	
US APPLICATION NO (If known, see 37 CFR 1.5)	
09/868930	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/00225	12 January 2000	15 January 1999

TITLE OF INVENTION

BENZENE-SULPHONAMIDE DERIVATIVES AND THEIR USES

APPLICANT(S) FOR DO/EO/US

Jacques DELARGE, Jean-Michel DOGNE and Bernard MASEREEL

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    International Search Report - EPO
    First Page of Publication
    International Preliminary Examination Report - with annexes

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	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) . . $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . $710.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$1000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$860.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☒ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**11** - 20 =	-0-	x $18.00	$	
Independent Claims	**1** - 3 =	-0-	x $80.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 990.00	
Reduction by 1/2, applicant qualifies for **small entity** status.				$ 495.00	
SUBTOTAL =				$ 495.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 495.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$	
TOTAL FEES ENCLOSED =				$ 495.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 495.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ ____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

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By _____
William E. Player
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Atty. Dkt. No. P66806US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Jacques DELARGE et al.

Appl. No.: New

Filed: July 16, 2001

For: BENZENE-SULPHONAMIDE DERIVATIVES AND THEIR USES

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

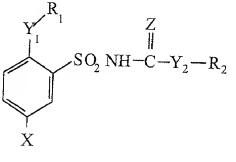
Enter the instant amendment before initial examination.

IN THE CLAIMS

Cancel claim 1-11, without prejudice or disclaimer, and add the following claims.

12. Benzene-sulphonamide derivates having the general formula (I):

(I)



in which:

X represents a nitro, cyano, halogen group, eventually radioactive .

Y_1 represents a secondary or tertiary amino group, a

sulphur or an oxygen

Y_2 represents a -NH group or nitrogen;

Z represents oxygen, sulphur, -N-CN or -CH-NO_2; and

R_1 and R_2, which can be identical or different, represent each independently a linear or ramified alkyl group, saturated or unsaturated with 2 to 12 carbon atoms, an alicyclic group, saturated or unsaturated with 3 to 12 carbon atoms, eventually radioactive, an aryl group, substituted or not by one or several alkyl groups in C_1-C_4, nitro, cyano, trifluoromethyl, carboxy and halogen groups, or an arylalkyl group,

or R_1 and/or R_2 form with Y_1 and/or Y_2 a 5 to 7 membered heterocyclic group, saturated or unsaturated

with the exception of derivatives for which X is a nitro group, . Y_1 represents a secondary amine group (-NH-), Y_2 represents a -NH group, Z an oxygen, R_2, an isopropyl and R_1 an element selected in a group constituted of (m-toluyl, phenyl and cyclooctyl) and with the exception of N-[(2-cyclooctylamino-5-cyanobenzene)sulfonyl] N'-isopropyl urea.

13. Derivate according to claim 12, characterized in that X represents nitro, cyano, bromo, iodine group.

14. Derivate according claim 12, characterized in that Y_1 represents a -NH group and Y_2 represents a -NH group or an oxygen atom.

15. Derivate according to claim 12, characterized in that R_1 and R_2 represent each independently an ethyl, butyl, tert-butyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl, decyl,

20. Pharmaceutical composition, characterized in that it includes a benzene sulphonamide derivate according to claim 12 in mixture with an acceptable pharmaceutical excipient and eventually other therapeutic agents.

21. Use of a derivate according to claim 12, for the production of a medicament for the treatment and/or the prevention of the illnesses involving the thromboxan A2, such as for cardio-vascular and blood, pulmonary, reproduction and renal use.

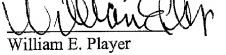
22. Use of a radiolabelled derivate according to claim 12, as binding to thromboxan A2 receptor.

REMARKS

Claims 12-22 replace claims 1-11, in order to delete multiple dependencies.

Favorable action is requested.

Respectfully submitted,

By: 

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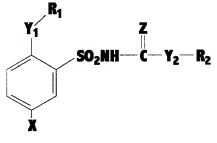
Benzene-sulphonamide derivatives and their uses

Technical domain

This invention relates to new benzene-sulphonamide derivatives and to their non-toxic salts as well as to their therapeutic uses.

Disclosure of the invention

The new benzene-sulphonamide derivatives, according to the invention, are represented by the general formula (I) :



(I)

in which:

X represents a nitro, cyano, halogen group, eventually radioactive .

Y_1 represents a secondary or tertiary amino group, a sulphur or an oxygen;

Y_2 represents a nitrogen, an oxygen or a -NH group;

Z represents oxygen, sulphur, -N-CN or $-CH-NO_2$; and

R_1 and R_2, which can be identical or different, represent each independently a linear or ramified alkyl group, saturated or unsaturated wit 2 to 12 carbon atoms, an alicyclic group, saturated or unsaturated with 3 to 12 carbon atoms, eventually radioactive, an aryl group, substituted or not by one or several alkyl groups in C_1-C_4, nitro, cyano, trifluoromethyl, carboxy and halogen, or an arylalkyl group,

or R_1 and/or R_2 form with Y_1 and/or Y_2 a 5 to 7 membered heterocyclic group, saturated or unsaturated chains.

with the exception of derivatives for which X is a nitro group, . Y_1 represents a secondary amine group (-NH-), Y_2 represents a -NH group, Z an oxygen, R_2 an isopropyl and R_1 an element selected in the group comprising (m-toluyl, phenyl and cyclooctyl) and with the exception of N-[(2-cyclooctylamino-5-cyanobenzene)sulfonyl]N'-isopropyl urea.

This invention refers also to optical isomers of benzene-sulphonamide derivatives covered by the formula (I) or to salts pharmacologically acceptable of these derivatives

This invention refers also to salts of these derivatives, covered by the formula (I), by addition of non-toxic basis, for example to sodium and potassic salts, to salts with an organic acid, as an amino acid such as the lysine, the arginine, for example.

When, in the general formula (I), one has an asymmetrical carbon atom (as for example when R_1 and/or R_2 represent an arylalkyl group), the invention refers as well as to pure optical isomers than to the racemic mixture.

Preferred classes of compounds according to the formula (I) are, especially, those in which the X represents a nitro, cyano, bromo or iodo group, Y_1 represents a -NH group, Y_2 represents a -NH group or an oxygen atom and R_1 and R_2 represent each independently an ethyl, butyl, tert-butyl propyl, isopropyl, pentyl, hexyl, heptyl, octyl, decyl, amyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclododecyl, 2-cyclohexenyl, m-toluyl, o-toluyl, p-toluyl, phenyl, allyl, adamantyl, norbornyl, caproyl, 3-carboxyphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, furfuryl, benzyl or 1-phenylethyl group.

Another preferred class of these compounds is that in which R_2 and Y_2 form a homopiperidin group and that in which R_1 and Y_1 form a morpholin or homopiperidin group.

Still another particularly interesting class is that made by radioactive derivatives of the invention, and especially the derivatives in which X represents radioactive iodine, such that the ^{126}I and its radioactive isotopes ^{125}I and ^{131}I, and those in which R_1 represents a saturated alicyclic group or unsaturated group with a tritium hydrogen in positions 2 and /or 3 of the cycle.

As one will see hereinafter in a more detailed way, the derivatives complying with the formula (I) are very useful in the prevention and/or treatment of illnesses involving the thromboxan A_2 at different levels, and especially in the cardio-vascular and blood domains, pulmonary domain, reproduction domain and renal domain. They constitute also an excellent radiolabelled pharmacological tool of the thromboxan A2 receptors.

The present invention concerns, therefore, also the use of these benzene-sulphonamide derivatives and their salts for drug manufacture for the treatment and/or the prevention of the illnesses involving the thromboxan A2 as well as as radiolabelled pharmacological tools of the thromboxan A2 receptors and of the pharmaceutical compositions containing these derivatives, these latter or their salts being used alone or in combination with excipients and/or other therapeutic agents having a similar or different activity.

The active compounds of the invention can be administered, according to the invention, under the form of a pharmaceutical composition, in association with different pharmaceutical excipients and this by oral, parenteral, rectal and topical way.

For the oral administration, one will use pills, granules, tablets, capsules, solutions, syrups, emulsions and suspensions containing classic excipients or additives in clinical pharmacy.

By parenteral way, the salts of active products could be administered in aqueous solution for example.

For the rectal administration, one will use suppositories and, by topical way, lotions, unguents, pomades, aerosols or nebulizers.

The active products can be used alone or in combination with other active products having a similar or different activity.

Among the compounds which give, in pharmaceutical use, very interesting results, we have to consider those in the formula (I), in which X represents a NO_2 or iodine group,

Y_1 represents a secondary amino group,

Y_2 represents a -NH group,

Z represents an oxygen group, sulphur group or -N-CN group,

and R_1 represents a cyclohexyl group, cycloheptyl group or cychlohexen-2-yl group, and

R_2 an isopropyl group, tert-butyl group, pentyl group or homopiperidin group,

and particularly considering the following compounds:

N-[(2-cyclohexylamin-5-nitrobenzene)sulfonyl]N'-tert-butyl urea,

N-cyano-N'-[(2-metatoluylamin-5-nitrobenzene)sulfonyl]homopiperidinoamidine,

N-[(2-cycloheptylamin-5-nitrobenzène)sulfonyl]N'-cyclohexyl thiourea, and

N-[(cyclohexen-2-yl)-5-iodobenzene)sulfonyl]N'-pentyl urea.

Best way to realize the invention

Hereafter the definitions and explanations related to the synthesis of the derivatives of the invention are given.

The evolution of most reactions is followed by thin layer chromatography (T.L.C..). The plates are constituted of aluminium foils covered with silica gel $60F_{254}$ (Merck®). The plate is examined by ultraviolet rays at 254 or 362 nm.

The elementary analysis (C, H, N, S) have been realized and correspond to the theoretic formula (+/-0,4%). The IR and [^{1}H]-RMN spectrums are in accordance with the proposed formulas.

The elementary analysis (C, H, N, S) have been determined on an Carlo Erba EA 1108 analizer .

The infrared spectrums of different substances (1 mg) have been registered by means of a FT-IR Perkin-Elmer 1750 under the form of KBr (250 mg) pellets.

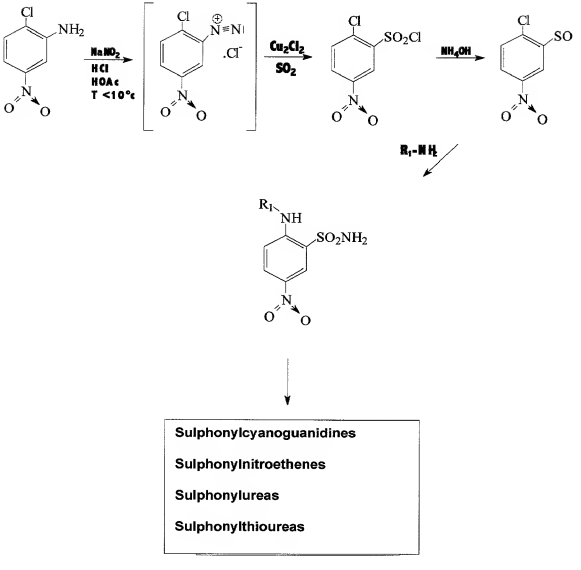
After dissolution in the deuterium DMSO, the RMN-^{1}H spectrum of different molecules is registered on an Bruker 400 apparatus.

The melting points of the obtained molecules have been determined on an Büchi-Tottoli apparatus.

The general formula compounds (I) can be obtained easily by different way summarized in the hereafter synthetic schemes.

Scheme 1

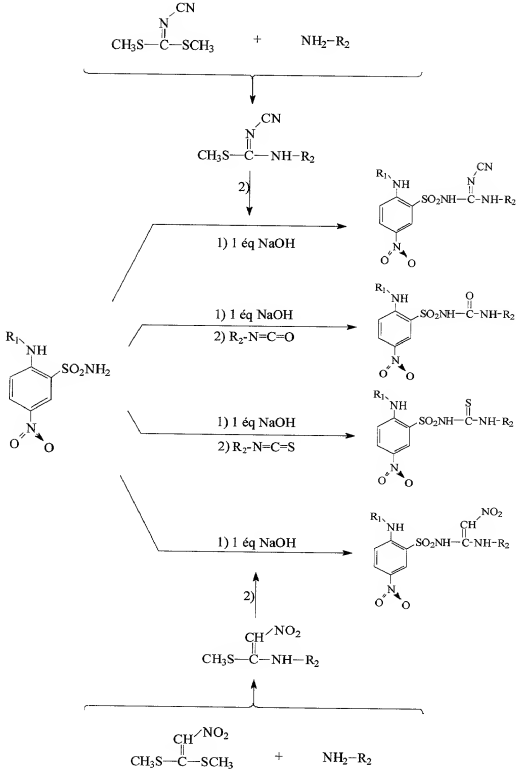
Nitrobenzene derivatives



The 2-chloro-5-nitroaniline is diazotised at a temperature comprised between 0 and 10°C. The diazonium salt formed is substituted in presence of copper salts (catalyst) by sulphur anhydride to generate sulphochloride which in presence of ammonia forms the corresponding 2-chloro-5-nitrobenzenesulfonamide. The chlorine is then substituted by an adequate amine.

The adequated sulphonylurea, thioureas, cyanoguanidines and nitroethenes functions are obtained by condensation of selected reactives (isocyanates for sulphonylureas or isothiocyanates for sulfonylthioureas) or prepared (N-cyano-N'-alkyl (or aryl)carbamimidothioate of S-methyl for sulfonylcyanoguanidines and 1-alkyl (or aryl)amino-1'-methylthio-2-nitroethylene for sulfonitroethenes) on the sulphonamide sodium salt obtained by reaction with exactly 1 sodium hydroxyde equivalent.

Scheme 1 (following)



1.1.) 2-Chloro-5-nitrobenzenesulfonamide

On the one hand, one saturates 160 ml of anhydrous acetic acid in SO_2 for 5 hours (solution A), on the other hand, 10 g of 2-chloro-5-nitroaniline are dissolved in 40 ml of 12 N hydrochloric acid and 100 ml of anhydrous acetic acid (solution B). This solution is cooled till reach a temperature near 0 to -5°C. Finally, one dissolves 7 g of sodium nitrite in 10 ml of water (solution C). The solution C is added drop by drop to solution B to form the diazonium salt. The temperature must be maintained towards -5°C. 4 g of $CuCl_2$ are dissolved in 10 ml of water (solution D). The solution D is added to solution A and agitated for 2 minutes. A precipitate of Cu_2Cl_2 appears. The diazonium solution is then prudently and under agitation added to this suspension then 180 g of ice is added in the reaction medium. The precipitate of sulphonyl chloride is rapidly collected on filter, washed with cold water and added under agitation to a previously cooled solution, realized with 50 ml of concentrated ammonia and 100 ml of water. After filtration and clarification with charcoal, the filtrate is concentrated under reduced pressure. The pH is adjusted to 5-6 by 10 N hydrochloric acid. After cooling, the sulphonamide is collected on filter, washed with water and dried. Then it is eventually recrystallized with methanol.

Yield: 50-60%.

Melting point: 178°C

Molecular Weight: 236,62 ($C_6H_5ClN_2O_4S$)

1.2.) 2-Alkyl (or aryl)amino-5-nitrobenzenesulfonamides

10 g of 2-chloro-5-nitrobenzènesulfonamide prepared in 1.1.) are put in solution in 50 ml of 3-chlorotoluene with 15 ml of amine. One heats about 3 hours, under nitrogen. The reaction is followed by thin layer chromatography. At the term, the solution is filtered, then concentrated under reduced pressure. The residue is retaken by a sodium hydroxyde solution at 2% and purified with charcoal. One brings to pH 1 by 2N

hydrochloric acid. The suspension is extracted three times by 100 ml of diethylic ether. The ether is evaporated under reduced pressure. The residue is retaken by a sodium hydroxyde solution at 2%, then clarified with charcoal and brought to pH 7,5-8 by 5N hydrochloric acid.

The precipitate of 2-alkyl (or aryl)amino-5-nitrobenzenesulfonamide is collected on filter, washed and recrystallized with methanol.

1.3.) Sulphonylureas

N-[(2-alkyl (or aryl)amino-5-nitrobenzene)sulfony]] N'-alkyl (or aryl) ureas

One dissolves 0,01 mole of suitable sulphonamide prepared in 1.2.) in 30 ml of a water-acetone mixture (50/50 vol/vol). After having added a sodium hydroxyde equivalent (solution at 10%), one adds 0,02 mole of adequate isocyanate. For weak volatile isocyanates (B.P. >90°C), the solution is brought to reflux under agitation while for volatile isocyanates (isopropyl-, ethyl-, methylisocyanate), the solution is placed under agitation at room temperature. The progression of the reaction is followed by thin layer chromatography. At the end, the reaction medium is evaporated under depression, the residue is retaken by 100 ml of sodium hydroxyde at 2%. This solution is extracted three times by 150 ml of diethylic ether then clarified with charcoal. The aqueous phase is brought to pH 7,5 by 2N hydrochloric acid. The sulphonylurea which precipitates is collected on filter, washed with water and dried. The product is eventually recrystallized in diluted alcohol.

Examples of compounds prepared according to this process (Table 1) :
n° 1; 2; 13; 17; 19; 20; 21; 22; 23; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 44; 46; 47; 48; 49; 50; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 67; 73; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 94; 95; 96.

1.4.) Sulfonylthioureas

N-[(2-alkyl (or aryl)amino-5-nitrobenzène)sulfonyl] N'-alkyl (or aryl) thioureas

0,01 mole of suitable sulphonamide prepared in 1.2.) is dissolved in 30 ml of a water-acetone mixture (50/50 vol/vol) . After having added a sodium hydroxyde equivalent (solution at 10%), 0,02 mole of adequate isothiocyanate is added. For weak volatile isothiocyanates (B.P.. >90°C), the solution is brought to reflux under agitation while for volatile isothiocyanates (isopropyl, ethyl, methylisothiocyanate), the solution is placed under agitation at room temperature. The progression of the reaction is followed by thin layer chromatography. At the end, the reaction medium is evaporated under depression, the residue is retaken by 100 ml of sodium hydroxyde at 2%. This solution is extracted three times by 150 ml of diethylic ether then clarified with charcoal. The aqueous phase is brought to pH 7,5 by 2N hydrochloric acid. The sulfonylthiourea which precipitates is collected on filter, washed with water and dried. The product is eventually recrystallized in diluted alcohol.

Examples of compounds prepared according to this process (Table 1) : n° 11; 12; 14; 15; 16; 35; 36; 37; 38; 39; 40; 41; 50.

1.5.) Sulfonylcyanoguanidines

1.5.1.) N-cyano-N'-alkyl (or aryl)carbamimidothioates of S-methyl

One allows to react 0,05 mole of dimethyl N-cyanodithioiminocarbonate with 0,075 mole of adequate amine in 10 ml of ethanol. This solution is heated under reflux for 15 to 20 hours (for volatile amine, the reaction itself will proceed at room temperature). The progression of the reaction is followed by thin layer chromatography. At the end, the solution is cooled under ice cold water and the precipitate collected on filter, then it is recrystallized into boiling methanol.

1.5.2.) N-[(2-alkyl (or aryl)amino-5-nitrobenzène)sulfonyl] N'-alkyl cyanoguanidines

0,01 mole of suitable sulphonamide prepared in 1.2.) is dissolved in 5 ml of a water-acetone mixture (50/50 vol/vol) and then 0,01 mole of sodium hydroxyde is added (solution at 10%). This solution is placed under agitation for 10 minutes then concentrated under reduced pressure. The residue (sulfonamidate) is solubilized in a mixture constituted of 3 ml of dioxane and 2 ml of dimethylformamide then added with 0,015 mole of adequate S-methyl-N-cyano-N'-alkylcarbamimidothioate prepared in 1.5.1.). This solution is brought to reflux under agitation. The progression of the reaction is followed by thin layer chromatography. At the end of the reaction, the solution is concentrated under reduced pressure then added with 100 ml of sodium hydroxyde at 2%. This solution is extracted three times by 150 ml of diethylic ether then clarified with charcoal. The aqueous phase is brought to pH 7,5 by hydrochloric acid 2N. The precipitate is collected on filter, washed with water and dried. The product is eventually recrystallized into methanol.

T.L.C. : ethyl acetate 13/cyclohexane 7.

Examples of compounds prepared according to this process (Table 1) : n° s 3; 4; 5; 6; 7; 8; 9; 18; 51; 74.

1.6.) Sulfonylnitroethenes

1.6.1.) 1-Alkyl (or aryl)amino-1'-methylthio-2-nitroethylnes

One allows to react 0,05 mole of 1,1'-bis(methylthio)-2-nitroethylene with 0,075 mole of adequate amine in 10 ml of ethanol. This solution is brought under reflux 15 to 20 hours (for volatile amine, the reaction itself will proceed to room temperature). The progression of the reaction is followed by thin layer chromatography. At the end, the solution is cooled

under ice cold water and added with 30 ml of water. The obtained precipitate is collected on filter, then recrystallized with boiling methanol.
T.L.C. : ethyl acetate 8/ petroleum ether PE 40/60 12.

1.6.2.) 1-Alkyl (or aryl)amino-1'-[2-alkyl (or aryl)amino-5'-nitrobenzenesulfonamide]-2-nitroethylnes

0,01 mole of suitable sulphonamide prepared in 1.2.) is dissolved in 5 ml of a water-acetone mixture (50/50 vol/vol), then 0,01 mole of sodium hydroxyde is added (solution at 10%). This solution is placed under agitation for 10 minutes then concentrated under reduced pressure. The residue (sulfonamidate) is solubilized in a mixture constituted of 3 ml of dioxane and 2 ml of dimethylformamide then added with 0,015 mole of 1-alkyl (or aryl)amino-1'-methylthio-2-nitroethylne adequately prepared in 1.6.1). This solution is brought to reflux under agitation. The progression of the reaction is followed by thin layer chromatography . At the end of the reaction, the solution is concentrated under reduced pressure then added with 100 ml of sodium hydroxyde at 2%. This solution is extracted three times with 150 ml of diethylic ether then clarified with charcoal. The aqueous phase is brought to pH 7,5 by 2N hydrochloric acid. The precipitate is collected on filter, washed with water and dried. The product is eventually recrystallized into methanol.
T.L.C. : ethyl acetate 8/ petroleum ether PE 40/60 12.

Composition example prepared following this process (Table 1) : n° 10.

1.7.) Sulfonylcarbamates

2-Alkyl (or aryl)amino-5-nitrobenzenesulfonylcarbamates of ethyl

0,01 mole of sulphonamide prepared in 1.2.) is dissolved in 10 ml of anhydrous pyridine. Under agitation, drop by drop, a large excess (10 ml) of ethyl chloroformiate is added. The evolution of the synthesis is

followed by thin layer chromatography. At the end of the reaction, about 15 minutes after having added the chloroformiate, the solution is evaporated under reduced pressure and the residue retaken by 100 ml of sodium hydroxyde at 2%. After two extractions by 150 ml of diethylic ether, the alkaline solution is clarified with charcoal then neutralized to pH 6,5 with 2N hydrochloric acid. The carbamate precipitate is collected, washed with water and dried under vacuum.

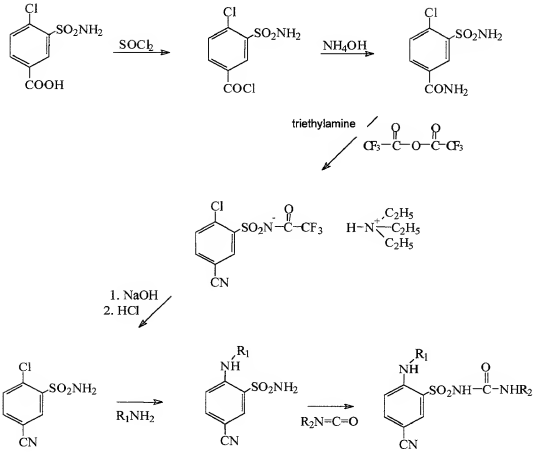
Yield: 75%-88%

T.L.C.: ethyl acetate, methanol and triethylamine 18/2/1.

Example of compounds prepared according to this process (Table 1) : n° 45.

Scheme 2

Derivatives of benzonitrile



The 4-chloro-3-sulfamoylbenzoic acid is put in reaction with the thionyl chloride to form the acid chloride which, in presence of ammonia, generates the corresponding carboxamide. The latter is dehydrated in presence of trifluoroacetic anhydride. The acylsulphonamide at the moment of this reaction is hydrolyzed in presence of exactly 2,5 sodium hydroxyde equivalent. The sulphonamide is then regenerated to pH acid. The chlorine is then substituted by an adequate amine. The sulphonylurea function is obtained by condensation of the isocyanate chosen on the previously sulphonamide sodium salt prepared by reaction with exactly 1 sodium hydroxyde equivalent. The carboxylic function is then regenerated by alkaline hydrolysis of the benzonitrile.

2.1.) 4-Chloro-3-sulfamoylbenzenecarboxamide

One allows to react 0,01 mole of acid 4-chloro-3-sulfamoylbenzoic with 25 ml of thionyl chloride. This solution is brought to reflux for 3 hours. At the end, the reaction medium is concentrated under reduced pressure, then added with 10 ml of dioxane. This solution is added under agitation at a previously cooled solution realized with 25 ml of concentrated ammonia and with 50 ml of water. The excess of ammonia is eliminated under reduced pressure. The precipitate is collected on filter, washed with water and dried. It is eventually recrystallized into methanol.

Yield:	50-60%
Point of fusion:	220-222°C
Molecular weight:	234,656 ($C_7H_7ClN_2O_3S$).
T.L.C.:	ethyl acetate 18/methanol 4/formic acid 5 drops.

2.2.) 4-Chloro-3-sulfamoylbenzonitrile

To 0,01 mole of 4-chloro-3-sulfamoylbenzenecarboxamide 80 ml of anhydrous tetrahydrofurane are added. This suspension is cooled at 0°C then successively added with 0,045 mole of triethylamine and 0,02 mole of

trifluoracetic anhydride. The progression of the reaction is followed by thin layer chromatography. At the end, the reaction medium is concentrated under depression. The residue is retaken by water, filtered and washed. The obtained product is put in reaction with 2,5 equivalent of 2N sodium hydroxyde solution for a maximum of 30 minutes. The solution is then brought to pH 1 by 2N hydrochloric acid. The precipitate is then rapidly collected on filter, washed with water and dried.

Yield:	70-80%
Melting point:	199-201°C
Molecular weight:	216,64 ($C_7H_5ClN_2O_2S$).
Elementary analysis: found:	+/- 0,4% of calculated.
T.L.C.:	ethyl acetate 18/methanol 4/ formic acid 5 drops.

2.3.) 4-Alkyl (or aryl)amino-3-sulfamoylbenzonitriles

One processes as in 1.2.) by using the 4-chloro-3-sulfamoylbenzonitrile as raw material.

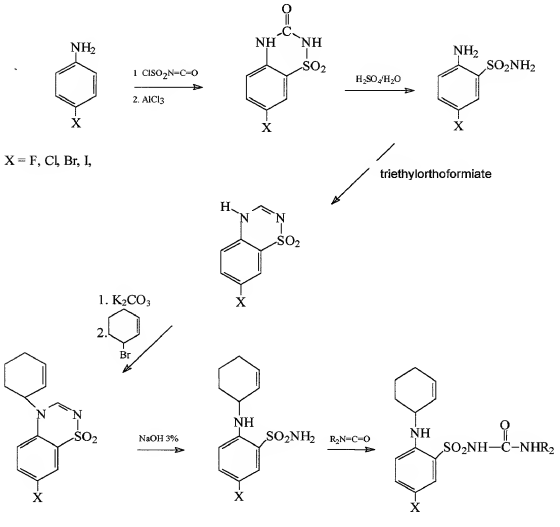
2.4.) N-[(2-alkyl (or aryl)amino-5-cyanobenzene)sulfonyl] N'-alkyl (or aryl) ureas

One processes as in 1.3.) by using 4-alkyl (or aryl)amino-3-sulfamoylbenzonitrile as raw material.

Examples of compounds prepared according to this process (Table 1) : n° 24; 43; 66; 97.

Scheme 3

Halogenobenzenic derivatives



Halogenobenzenic derivatives

The adequate aniline is placed in reaction with a light excess of chlorosulfonylisocyanate at a temperature of -5°C. Aluminium chloride is then added in the medium in order to obtain the following cyclic product: 2,3-dihydro-7-halogeno-3-oxo-4H-1,2,4-benzothiazidine 1,1-dioxyde. The

latter is hydrolyzed by treatment in sulphuric medium. The aminosulfonamide is then engaged in a new reaction of cyclisation to the triethyl orthoformiate. The 7-halogeno-4H-1,2,4-benzothiadiazine 1,1-dioxide obtained is alkyled in position 4 with the 3-bromocyclohexene in presence of 4 potassic carbonate equivalent.

The 2-(cyclohexene-2-yl)amino-5-halogenobenzenesulfonamide is then generated by sodium hydroxyde treatment. The sulphonylurea function is obtained by condensation of the chosen isocyanate on the previously sulphonamide sodium salt prepared by reaction with exactly 1 sodium hydroxyde equivalent.

3.1.) 2,3-Dihydro-7-halogeno-3-oxo-4H-1,2,4-benzothiadiazine 1,1-dioxydes

0,07 mole of chlorosulfonylisocyanate is solubilised in 90 ml of nitromethane previously cooled at -5°C, then drop by drop, 50 ml of a solution of nitromethane containing 0,06 mole of adequate amine, is added. One add drop by drop 0,097 mole of aluminium chloride in the medium. The solution is heated under reflux for 45 minutes, then poured on ice. The obtained precipitate is collected on filter, washed with water and dried. The product is eventually purified by redissolution in a sodium bicarbonate aqueous solution (5% m/vol) and reprecipitation by 2N hydrochloric acid addition.

Yield: 70-75%

T.L.C.: ethyl acetate 20/formic acid 5 drops.

3.2.) 2-Amino-5-halogenobenzenesulfonamides

0,01 mole of 2,3-dihydro-7-halogeno-3-oxo-4H-1,2,4-benzothiadiazine 1,1-dioxyde prepared in 5.1.) is added to 100 ml of a sulphuric- acid water mixture (50/50). The reaction medium is carried to reflux for one hour. After cooling, the solution is brought to pH 3 by sodium

hydroxyde at 30%. The obtained precipitate is collected on filter, washed with water and dried.

Yield: 80-85%

T.L.C.: ethyl acetate 13/cyclohexane 7/formic acid
5 drops.

3.3.) 7-Halogeno-4H-1,2,4-benzothiadiazine 1,1- dioxides

0,01 mole of 2-amino-5-halogenobenzenesulfonamide prepared in 5.2.) is dissolved in 25 ml of triethylorthoformiate. The reaction medium is carried to reflux for one hour. After cooling, the precipitate is collected on filter, washed and dried.

Yield: 50-60%

T.L.C.: ethyl acetate 13/cyclohexane 7/formic acid
5 drops.

3.4.) 4-(Cyclohexen-2-yl)-7-halogeno-1,2,4- benzothiadiazine 1,1-dioxydes

One puts in suspension 0,01 mole of 7-halogen-4H-1,2,4-benzothiadiazine 1,1-dioxide prepared in 5.3.) in 300 ml of acetonitrile containing 0,04 mole of potassic carbonate. The reaction medium is carried to reflux 30 minutes then added with 0,04 mole of 3-bromocyclohexene. The reflux is maintained during 4 hours. The reaction is followed by thin layer chromatography. At the end, the potassic carbonate in excess is collected on filter. The filtrate is concentrated under reduced pressure. The residue is added with 50 ml of methanol carried to ebullition. The precipitate is collected on filter, washed and dried.

Yield: 60-70%

T.L.C.: ethyl acetate 13/cyclohexane 7/formic acid
5 drops.

3.5.) 2-(Cyclohexen-2-yl)amino-5-halogenobenzene-sulphonamides

To 0,01 mole of 4-(cyclohexen-2-yl)-7-halogeno-1,2,4-benzothiadiazine 1,1-dioxide prepared in 5.4) is added 50 ml of sodium hydroxyde at 3%. The suspension is brought to 60°C for twelve hours. At

the end, the solution is brought to pH 7 by 5 N hydrochloric acid . The obtained precipitate is collected on filter, washed with water and dried.

Yield: 50-60%

T.L.C.: ethyl acetate 13/cyclohexane 7/formic acid

5 drops.

3.6.) N-[(2-cyclohexen-2-yl)-5-halogenobenzene)sulfonyl] N'-alkyl (or aryl)urea

One processes as in 1.3.) by using 2-(cyclohexen-2-yl)amino-5-halogenobenzenesulfonamide as raw material.

Examples of compounds prepared according to this method (Table 1): n° 68; 69; 70; 71; 72.

The Table 1 given hereinafter refers to preparation of a composed series complying with the general formula (I).

As already specified, the new benzene-sulphonamide derivatives so described are interesting in prevention and/or the treatment of the illnesses involving thromboxan A_2 at different levels and especially:

Cardio-vascular and blood diseases:

-Myocardial infarction,

-Thrombus formation and vascular lesions,

-Haemostasis diseases,

-Atherosclerosis,

-Arteriosclerosis,

-Myocardial ischemia,

-Arterial hypertension.

Pulmonary:

-Asthma,

-Bronchospasm,

-Pulmonary hypertension.

Of the reproduction:

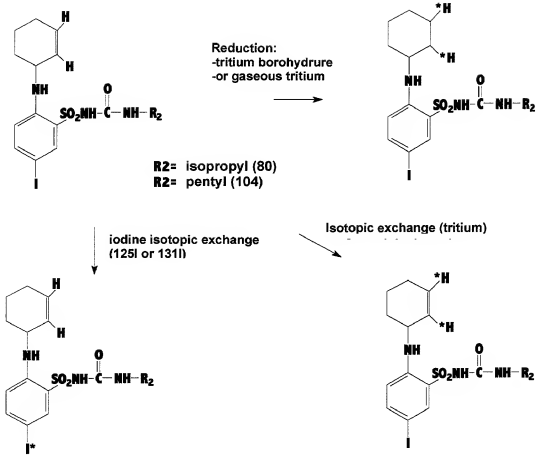
-Preeclampsia.

Renal:

-Renal hypertension,

-Renal dysfunction.

The derivatives of the invention are also interesting for the conception of an original radiolabelled pharmacological tool of thromboxan A2 receptors. The following scheme 6 shows this kind of application from the compounds n° 80 and 104 (Table 1).



As we can see, two labelling technics are considered:

- A tritium marking technique (^{3}H).

  - either by reduction with a tritium reducer: (tritium hydrogen or tritium borohydrure).

  - either by isotope exchange.

- An iodine labelling technic (^{125}I or ^{131}I) by isotope exchange.

What follows and the tables hereinafter refer to results of pharmacological tests realised on a certain number of compounds given into Table 1.

To operate a first selection, the capacity of these compounds to displace in a specific way a tritium ligand, the [^{3}H] SQ-29.548, from the thomboxan A_2 receptor of human platelets have been examined. This binding test is, in fact, simple, fast and allows so a selection of products which have a strong affinity for thromboxan A2 platelet receptors (TPα).

The TXA_2 antagonist potency of the selected compounds has been evaluated by a platelet aggregation test induced by the U-46619 (stable agonist of the thromboxan A2) or by the arachidonic acid.

Two tests on smooth musculature have allowed to confirm the antagonist potency on the TPτ thromboxan A2 receptors. Indeed, the capacity of the selected compounds during the binding to prevent the contraction of the rat fundus induced by l'U-46619 and to relax the rat aorta precontracted by this same stable agonist of the TXA_2 have been evaluated;

All the results are recorded in parallel with those of two thromboxan A2 receptors antagonists described in literature and which are the object of in-depth clinical studies: the sulotroban and the SQ-29.548.

The SQ-29.548 and the U-46619 are respectively the acid [15-[1-alpha,2-beta (5Z),3-beta,4-alpha]-7-[3-[[2-(phenylamino)carbonyl]hydrazin]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic and the 9,11-didesoxy,11-alpha,9-alpha-epoxy-methanoprostaglandine F_{2a}.

The materials and methods used for pharmacological tests are those described in literature.

TABLE 2

Binding to human platelets thromboxane A_2 receptors

Binding Test Results on human platelets

COMPOUND NUMBER	BINDING TEST		
	10^{-6}M : (%)[1] AFFINITY	10^{-7}M : (%)[1] AFFINITY	IC 50[2] (ηM)
SULOTROBAN	55,6	16,5	1100
SQ-29.548	100	72,0	23,2
1	93,6	68,0	
2	67,7		
3	20,1		
4	50,0		
5	72,1		
6	29,8		
7	42,9		
8	33,0		
9	15,4		
10	57,7		
11	63,7		
12	67,2		
13	97,7	60,3	
14	92,9	34,0	
15	81,0	16,6	
16	100	46,1	
17	100	88,0	22,7
18	100	88,9	24,2
19	97,8	93,3	3,96
20	1,6		
21	92,2	44,2	
			STANDARD DEVIATION <5%

TABLE 2 (following)

COMPOUND NUMBER	BINDING TEST		
	10^{-6}M : (%)[1] AFFINITY	10^{-7}M : (%)[1] AFFINITY	IC 50[2] (ηM)
22	100	84,1	41,7
23	95,5	62,9	
24	73,7		
25	100	95,2	10,5
26	94,3	93,3	16,9
27	79,6		
28	81,9	39,6	
29	97,4	95,4	7,8
30	95,1	80,8	
31	80,5	42,2	
32	86,7	46,0	
33	86,6	52,4	
34	77,3		
35	45,0		
36	75,6		
37	72,3		
38	77,2		
39	74,5		
40	94,4	63,0	26,9
41	75,9		
42	92,3	50,5	
43	50,0		
44	80,2	51,3	
45	79,9	50,4	
STANDARD DEVIATION <5%			

TABLE 2 (following)

COMPOUND NUMBER	BINDING TEST		
	10^{-6}M : (%)[1] AFFINITY	10^{-7}M : (%)[1] AFFINITY	IC 50[2] (ηM)
46	1,4		
47	98,7	89,4	
48	51,9		
49	98,3	94,9	2,0
50	95,7	76,0	
51	64,7		
52	99,0	93,9	2,8
53	36,5		
54	91,7		
55	98,2	93,3	3,4
56	0,0		
57	67,0		
58	83,2		
59	92,2		
60	79,1		
61	98,6	94,8	1,1
62	3,7		
63	7,5		
64	57,8		
65	46,6		
66	49,6		
67	98,3	95,8	1,3
68	93,2	67,4	
69	13,2		
DEVIATION STANDARD <5%			

TABLE 2 (following)

COMPOUND NUMBER	BINDING TEST		
	10^{-6}M : (%)[1] AFFINITY	10^{-7}M : (%)[1] AFFINITY	IC 50[2] (ηM)
70	63,8		
71	77,8		
72	86,5	52,7	
73	98,3	95,6	1,2
74	90,9		
75	93,1		
76	97,6	93,5	3,5
77	79,4		
78	95,3	71,6	4,2
79	96,6		
80	98,6	97,9	2,4
81	93,3	65,0	57,8
82	98,5	98,0	4,5
83	98,5	92,7	4,5
84	96,9	73,7	23,9
85	92,9	42,5	107,2
86	98,4	94,3	1,83
87	95,6	76,0	18,1
88	95,4	82,0	16,2
89	96,6	83,5	11,5
90	96,9	88,6	5,46
91	97,3	90,8	3,31
92	98,8	95,2	1,62
DEVIATION STANDARD <5%			

TABLE 2 (following)

COMPOUND NUMBER	BINDING TEST		
	10^{-6}M : (%)[1] AFFINITY	10^{-7}M : (%)[1] AFFINITY	IC 50[2] (ηM)
93	97,9	90,2	7,8
94	98,4		2,82
95	98,5		1,45
96	92,3		43,95
97	89,7		98,48
			DEVIATION STANDARD <5%

1 Affinity means the per cent of [^{3}H]SQ-29.548 specifically substituted by the examined compound.

2 IC 50 : Means the concentrations required for replacing 50% of [^{3}H]SQ-29.548 bound to receptors TPα.

Test according to :

Cozzi P., Giordani A., Menichincheri M., Pillan A., Pinciroli V., Rossi A., Tonani R., Volpi D., Tamburin M., Ferrario R., Fusar D., Salvati P., - Agents combining thromboxane receptor antagonism with thromboxane synthase inhibition : [[[2-(1H-imidazol-1-yl)ethylidene]amino]oxy]alkanoic acids. - *J. Med. Chem.,* **1994**, 37, 3588-3604.

TABLE 3 : Platelet Aggregation
Test Results on Human Platelets aggregation

COMPOUND	AGGREGATION PLATELET TEST	
	ARACHIDONIC ACID IC 50[1] (µM)	U-46.619 IC 50[1] (µM)
SULOTROBAN	11,7	10,5
SQ-29.548	0,035	0,034
18	0,36	0,48
		STANDARD DEVIATION <5%

1IC 50 : Means concentrations required for reduction by 50% the platelet aggregation induced by 0,6 nM of arachidonic acid (AA) or by 30 nM of U-46619.

Test described according to :

Born G.V.R., Cross M. J., - The aggregation of blood platelets. - *J. Physiol.*, **1963**, 168, 178-195.

Tsuyoshi T., Masayuki Y., Shuichi W., Kazuhiro K., Takashi Y., - Designe, synthesis, and pharmacology of 3-substituted sodium azulene - 1 sulfonates and related compounds : Non-prostaboid thromboxane A_2 receptor antagonists. - *J. Med. Chem.*, **1993**, 36, 791-800.

TABLE 4 : Rat Aorta Contraction

Test results of Rat Aorta Contraction

COMPOUND	AORTA RAT CONTRACTION TEST IC 50 [1] (ηM)
SULOTROBAN	$1,6.10^{3}$
SQ-29.548	31,8
17	1,38
18	1,21
22	37,6
25	19,7
29	20,6
40	17,7
	STANDARD DEVIATION <5%

1IC 50 : Means the compounds concentrations reducing by 50% the Rat Aorta muscular tonus induced by U-46619 (0,03 µM).

Test described according to :

de Tullio P., Pirotte B., Lebrun P., Fontaine J., Dupont L., Antoine M. H., Ouedraogo R., Khelili S., Maggetto C., Masereel B., Diouf O., Podona T., Delarge J., 3-and-4-substituted 4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxides as potassium channels openers : synthesis pharmacological evaluation, and structure-activity relationships. - *J. Med. Chem.,* **1996**, 39, 937-948.

TABLE 5 : Rat Fundus Contraction
Test Results for preventing contraction of rat fundus

COMPOUND	TEST FOR PROVENTING THE RAT FUNDUS CONTRACTION IC 50 [1] (µM)
SULOTROBAN	0,83
SQ-29.548	0,18
18	0,07
	STANDARD DEVIATION <5%

1IC 50 : Means compounds concentrations reducing of 50% of maximum contraction amplitude caused by 5 µg de U-46619.

Test description according to :

Harris N., Greenberg R., Phillips M. B., Michel I. M., Goldenberg H. J., Haslanger M. F., Steinbacher T.E., - Effects of SQ-27,427, a thromboxane A2 receptor antagonist, in the human platelet and isolated smooth muscle. - *Eur. J. Pharmacol.,* **1984**, 103, 9-18.

TABLE 1

COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
1	1.3.	NO_2	NH	NH	O	cycloheptyl	isopropyl	153-155	74,6
2	1.3.	NO_2	NH	NH	O	cyclopentyl	isopropyl	141-143	72,3
3	1.5.2.	NO_2	NH	NH	N-CN	m-toluyl	isopropyl	170-172	62,0
4	1.5.2.	NO_2	NH	NH	N-CN	cyclopentyl	cyclohexyl	172-174	51,5
5	1.5.2.	NO_2	NH	NH	N-CN	cyclohexyl	cyclohexyl	179-181	58,7
6	1.5.2.	NO_2	NH	NH	N-CN	m-toluyl	cyclohexyl	175-177	33,7
7	1.5.2.	NO_2	NH	NH	N-CN	cyclohexyl	isopropyl	168-170	32,2
8	1.5.2.	NO_2	NH	NH	N-CN	cycloheptyl	isopropyl	153-155	46,0
9	1.5.2.	NO_2	NH	NH	N-CN	cyclooctyl	isopropyl	148-150	36,2
10	1.6.2.	NO_2	NH	NH	$CH\text{-}NO_2$	m-toluyl	cyclohexyl	176-178	46,5
11	1.4.	NO_2	NH	NH	S	m-toluyl	isopropyl	134-136	60,8
12	1.4.	NO_2	NH	NH	S	cycloheptyl	isopropyl	146-148	66,5
13	1.3.	NO_2	NH	NH	O	cyclohexyl	isopropyl	149-151	70,1
14	1.4.	NO_2	NH	NH	S	cyclohexyl	isopropyl	140-142	34,4
15	1.4.	NO_2	NH	NH	S	cyclooctyl	isopropyl	160-162	52,5
16	1.4.	NO_2	NH	NH	S	cyclohexyl	cyclohexyl	167-169	40,8

TABLE 1 (following)

COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
17	1.3.	NO_2	NH	NH	O	cyclohexyl	cyclohexyl	181-183	50,2
18	1.5.2.	NO_2	NH	---	N-CN	m-toluyl	[homopiperidine]	161-163	5,4
19	1.3.	NO_2	NH	NH	O	m-toluyl	tert-butyl	81-83	75,2
20	1.3.	NO_2	NH	NH	O	propyl	isopropyl	138-140	80,8
21	1.3.	NO_2	NH	NH	O	benzyl	isopropyl	144-146	74,3
22	1.3.	NO_2	NH	NH	O	cycloheptyl	cyclohexyl	174-176	48,8
23	1.3.	NO_2	NH	NH	O	cyclooctyl	cyclohexyl	150-152	45,4
24	2.4.	CN	NH	NH	O	m-toluyl	isopropyl	133-135	28,3
25	1.3.	NO_2	NH	NH	O	cycloheptyl	tert-butyl	135-137	68,2
26	1.3.	NO_2	NH	NH	O	cyclooctyl	tert-butyl	136-138	61,3
27	1.3.	NO_2	NH	NH	O	cyclohexyl	ethyl	163-164	72,2
28	1.3.	NO_2	NH	NH	O	cycloheptyl	ethyl	153-155	74,3
29	1.3.	NO_2	NH	NH	O	cyclohexyl	tert-butyl	147-149	70,2
30	1.3.	NO_2	NH	NH	O	o-toluyl	isopropyl	109-111	74,3
31	1.3.	NO_2	NH	NH	O	phenyl	allyl	150-152	53,2
32	1.3.	NO_2	NH	NH	O	cyclohexyl	allyl	152-154	56,3

TABLE 1 (following)

COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
33	1.3.	NO_2	NH	NH	O	cycloheptyl	allyl	138-140	58,2
34	1.3.	NO_2	NH	NH	O	cyclooctyl	allyl	159-161	47,3
35	1.4.	NO_2	NH	NH	S	propyl	isopropyl	151-153	72,7
36	1.4.	NO_2	NH	NH	S	benzyl	isopropyl	149-151	62,8
37	1.4.	NO_2	NH	NH	S	cyclopentyl	isopropyl	156-158	68,9
38	1.4.	NO_2	NH	NH	S	cyclohexyl	isopropyl	149-151	63,7
39	1.4.	NO_2	NH	NH	S	cycloheptyl	ethyl	162-164	62,4
40	1.4.	NO_2	NH	NH	S	cycloheptyl	cyclohexyl	172-174	38,3
41	1.4.	NO_2	NH	NH	S	cyclooctyl	cyclohexyl	177-179	30,3
42	1.4.	NO_2	NH	NH	S	cyclohexyl	furfuryl	168-169	27,2
43	2.4.	CN	NH	NH	O	cyclohexyl	isopropyl	148-150	32,3
44	1.3.	NO_2	NH	NH	O	cyclooctyl	ethyl	154-155	60,8
45	1.7.	NO_2	NH	O	O	cyclopentyl	ethyl	147-149	27,4
46	1.3.	NO_2	NH	NH	O	caproyl	isopropyl	132-134	25,8
47	1.3.	NO_2	NH	NH	O	adamantyl	tert-butyl	169-171	54,3
48	1.3.	NO_2	NH	NH	O	cyclododecyl	isopropyl	162-164	50,8

TABLE 1 (following)

COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
49	1.3.	NO_2	NH	NH	O	2,3-dimethylphenyl	isopropyl	146-148	28,3
50	1.3.	NO_2	NH	NH	O	p-toluyl	isopropyl	132-134	70,8
51	1.5.2.	NO_2	NH	NH	N-CN	m-toluyl	tert-butyl	180-182	25,3
52	1.3.	NO_2	NH	NH	O	o-toluyl	tert-butyl	90-92	71,4
53	1.3.	NO_2	NH	NH	O	3-carboxyphenyl	isopropyl	167-169	24,2
54	1.3.	NO_2	NH	NH	O	norbornyl	isopropyl	177-179	48,3
55	1.3.	NO_2	NH	NH	O	norbornyl	tert-butyl	111-113	45,4
56	1.3.	NO_2	NH	NH	O	tert-butyl	isopropyl	165-167	58,3
57	1.3.	NO_2	NH	NH	O	hexyl	isopropyl	126-128	75,4
58	1.3.	NO_2	NH	NH	O	adamantyl	isopropyl	179-181	43,8
59	1.3.	NO_2	NH	NH	O	hexyl	tert-butyl	112-114	72,8
60	1.3.	NO_2	NH	NH	O	decyl	isopropyl	99-101	58,3
61	1.3.	NO_2	NH	NH	O	cyclohexyl	pentyl	138-140	60,2
62	1.3.	NO_2	---	NH	O	[morpholine]	isopropyl	183-185	28,3
63	1.3.	NO_2	---	NH	O	[morpholine]	tert-butyl	172-174	25,4
64	1.3.	NO_2	---	NH	O	[homopiperidine]	isopropyl	110-112	22,1

TABLE 1 (following)

COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
65	1.3.	NO_2	NH	NH	O	cyclohexyl	phenyl	178-180	27,4
66	2.4.	CN	NH	NH	O	norbornyl	isopropyl	149-151	24,7
67	1.3.	NO_2	NH	NH	O	p-toluyl	tert-butyl	126-128	64,3
68	3.6.	NO_2	NH	NH	O	2-cyclohexenyl	isopropyl	156-158	23,8
69	3.6.	F	NH	NH	O	2-cyclohexenyl	isopropyl	127-129	12,8
70	3.6.	CL	NH	NH	O	2-cyclohexenyl	isopropyl	132-134	15,3
71	3.6.	BR	NH	NH	O	2-cyclohexenyl	isopropyl	143-145	18,4
72	3.6.	I	NH	NH	O	2-cyclohexenyl	isopropyl	148-150	17,6
73	1.3.	NO_2	NH	NH	O	2,3-dimethylphenyl	tert-butyl	159-161	24,8
74	1.5.2.	NO_2	NH	NH	N-CN	cyclohexyl	tert-butyl	192-194	35,8
75	1.3.	NO_2	NH	NH	O	1-phenylthyl (rac.)	isopropyl	108-110	38,4
76	1.3.	NO_2	NH	NH	O	1-phenylthyl(rac.)	tert-butyl	146-148	35,2
77	1.3.	NO_2	NH	NH	O	1-phenylthyl (S)	isopropyl	108-110	28,3
78	1.3.	NO_2	NH	NH	O	1-phenylthyl (S)	tert-butyl	113-115	25,4
79	1.3.	NO_2	NH	NH	O	1-phenylthyl (R)	isopropyl	108-110	23,1
80	1.3.	NO_2	NH	NH	O	1-phenylthyl (R)	tert-butyl	113-115	22,8

TABLE 1 (following)

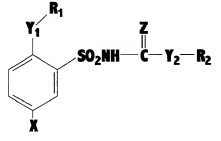
COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
81	1.3.	NO_2	NH	NH	O	cyclohexyl	propyl	137-139	78,8
82	1.3.	NO_2	NH	NH	O	cyclohexyl	butyl	158-160	72,1
83	1.3.	NO_2	NH	NH	O	cyclohexyl	hexyl	115-117	70,8
84	1.3.	NO_2	NH	NH	O	cyclohexyl	heptyl	117-119	76,3
85	1.3.	NO_2	NH	NH	O	cyclohexyl	octyl	93-95	65,4
86	1.3.	NO_2	NH	NH	O	2,4,6-trimethylphenyl	isopropyl	170-172	20,8
87	1.3.	NO_2	NH	NH	O	3,4-dimethylphenyl	isopropyl	149-151	35,4
88	1.3.	NO_2	NH	NH	O	3,5-dimethylphenyl	isopropyl	147-149	18,8
89	1.3.	NO_2	NH	NH	O	2,5-dimethylphenyl	isopropyl	148-150	27,3
90	1.3.	NO_2	NH	NH	O	2,4-dimethylphenyl	isopropyl	162-164	35,4
91	1.3.	NO_2	NH	NH	O	2,6-dimethylphenyl	isopropyl	148-150	20,2
92	1.3.	NO_2	NH	NH	O	2,4,6-trimethylphenyl	pentyl	146-148	18,2
93	3.6.	I	NH	NH	O	2-cyclohexenyl	pentyl	148-150	14,3
94	1.3.	NO_2	NH	NH	O	o-toluyl	pentyl	127-129	68,4

TABLE 1 (following)

COMPOUND NUMBER	SYNTHESIS METHOD	X	Y_1	Y_2	Z	R_1	R_2	PF, °C	YIELDING, (%)
95	1.3.	NO_2	NH	NH	O	p-toluyl	pentyl	146-148	70,1
96	1.3.	NO_2	NH	NH	O	m-toluyl	pentyl	129-131	71,2
97	2.4.	CN	NH	NH	O	cyclohexyl	pentyl	144-146	27,8

CLAIMS

1.- Benzene-sulphonamide derivates having the general formula (I):

(I) 

in which:

X represents a nitro, cyano, halogen group, eventually radioactive .

Y_1 represents a secondary or tertiary amino group, a sulphur or an oxygen

Y_2 represents a -NH group ,a nitrogen or an oxygen ;

Z represents oxygen, sulphur, -N-CN or -CH-NO_2; and

R_1 and R_2, which can be identical or different, represent each independently a linear or ramified alkyl group, saturated or unsaturated with 2 to 12 carbon atoms, an alicyclic group, saturated or unsaturated with 3 to 12 carbon atoms, eventually radioactive, an aryl group, substituted or not by one or several alkyl groups in C_1-C_4, nitro, cyano, trifluoromethyl, carboxy and halogen groups, or an arylalkyl group,

or R_1 and/or R_2 form with Y_1 and/or Y_2 a 5 to 7 membered heterocyclic group, saturated or unsaturated

with the exception of derivatives for which X is a nitro group, . Y_1 represents a secondary amine group (-NH-), Y_2 represents a -NH group, Z an oxygen, R_2, an isopropyl and R_1 an element selected in a group constituted of (m-toluyl, phenyl and cyclooctyl) and with the exception of N-[(2-CYCLOOCTYLAMiNO-5-CYANOBeNZeNe)SULFONYL] N'-isopropyl urea. ;

2.- Derivate according to claim 1, characterized in that X represents nitro, cyano, bromo, iodine group.

3.- Derivate according to one or the other claims 1 and 2, characterized in that Y_1 represents a -NH group and Y_2 represents a -NH group or an oxygen atom.

4.- Derivate according to any of claims 1 to 3, characterized in that R_1 and R_2 represent each independently an ethyl, butyl, tert-butyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl, decyl, amyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclododecyl, 2-cyclohexenyl, m-toluyl, o-toluyl, p-toluyl, phenyl, allyl, adamantyl, norbornyl; caproyl, 3-carboxyphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, furfuryl, benzyl or 1-phenylthyl group.

5.- Derivate according to one or the other claims 1 and 2, characterized in that R_2 and Y_2 form a homopiperidin group.

6.- Derivate according to one or the other claims 1 and 2, characterized in that R_1 and Y_1 form a morpholin or homopiperidin group.

7.- Derivate according to any of claims 1 to 6, characterized in that it is constituted by a salt chosen into the group formed by sodium salts, the potassic salts and the amino acid salts such as lysine, arginine.

8.- Derivate according to any of claims 1 to 7, characterized in that it is chosen in a group having:

N-[(2-cyclohexylamino-5-nitrobenzene)sulfonyl]N'-tert-butyl urea,

N-cyano-N'-[(2-metatoluylamino-5-nitrobenzene)sulfonyl]homopiperidinoamidine,

N-[(2-cycloheptylamino-5-nitrobenzene)sulfonyl]N'-cyclohexyl thiourea, and

N-[(cyclohexen-2-yl)-5-iodobenzene)sulfonyl]N'-pentyl urea.

9.- Pharmaceutical composition, characterized in that it includes a benzene sulphonamide derivate according to any of claims 1 to 8 in

mixture with an acceptable pharmaceutical excipient and eventually other therapeutic agents.

10.- Use of a derivate according to any of claims 1 to 8, for the production of a medicament for the treatment and/or the prevention of the illnesses involving the thromboxan A2 , such as for cardio-vascular and blood , pulmonary, reproduction and renal use.

11.- Use of a derivate according to any of claims 1 to 8, as radiolabelled pharmacological tool of the thromboxan A2 receptors.

INSTRUCTIONS FOR THE COMPLETION OF SMALL ENTITY DECLARATION

Check box (1) if for use with application about to be filed.
Check box (2) or (3) if for use with application already on file or Patent and complete U.S. Serial No. and Filing Date, or Patent No. and issue date, if known.

CHECK ONLY ONE OF BOXES 4, 5 OR 6, WHICHEVER IS APPLICABLE

Check box (4), individuals who are either: (a) an inventor or (b) a person who would qualify as an independent inventor had he/she made the invention, must sign and date at (8), if he/she have not, and are under no obligation to assign, grant, convey or license any right in the invention to any person who could not likewise be classified as an independent inventor if that person had made the invention or to any concern which would not qualify as a small business concern or non-profit organization (see below).

Check box (5), date, complete name of small business concern and authorized signatory, sign and complete his/her title at (9), if small entity status is claimed by virtue of inventor(s) rights having been, or being obligated to assign, grant, convey or license, to a concern whose number of employees, including those of its affiliates, does not exceed 500 persons. Concerns are affiliates when either controls, directly or indirectly, or has the power to control, the other, or a third party has the power to control both. Number of employees is average over fiscal year of those employed during each pay period, including full-time, part-time or temporary employees. If the small business concern has or is under obligation by contract or law to transfer any rights to another who cannot qualify as small entity, then small entity status not applicable.

Check box (6) and subsection (a), (b), (c) or (d), date, complete name of the nonprofit organization and authorized signatory sign and complete his/her title at (9), if small entity status is claimed by virtue of inventor(s) rights having been, or being obligated to, assign, grant, convey or license, to a nonprofit organization. Subsection (6)(a) to be checked if organization is university or other institution of higher learning; (6)(b) to be checked if organization of type described in Section 501(c)(3) of IRS Code and exempt from taxation under Section 501(a); (6)(c) to be checked if organization is nonprofit scientific or educational organization qualified under a statute of State of the U.S.; and (6)(d) to be checked if foreign organization and would qualify under (6)(b) or (6)(c) if such organization was located in the U.S.A. Fill in the State law under which the organization would qualify.

Check box (7)(a) or (b) as the facts dictate.

IMPORTANT

(1) Note that U.S. attorneys and agents cannot complete this document after signed. Therefore please completely fill it in before sending to us.

(2) Each person, concern or organization that has an interest in this invention must sign one of the "Small Entity" Declarations. For example, if an inventor/employee has an obligation to assign to his employer, a corporation having fewer than 500 employees, which corporation has licensed this invention to a licensee corporation also having less than 500 employees, then three "Small Entity" declarations are necessary before the lesser fee can be paid: one from the inventor; one from an official of the employer; and one from an official of the licensee. In the declarations by the inventors and the employer paragraph 7(b) would have to be checked and filled in, the licensee would check paragraph 7(a).

We will be pleased to answer your questions. You may contact us in the following ways:

JACOBSON, PRICE, HOLMAN & STERN

TELEPHONE: (202) 638-6666
TELFAX: (202) 393-5350
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THE JENIFER BUILDING

400 SEVENTH STREET N W.

WASHINGTON, D C 20004

Attny's Docket No. _____

SMALL ENTITY DECLARATION
[37 CFR 1.9(c-f)]

Each undersigned declares that

(1) ☒ the application attached hereto

(2) ☐ U S. Application Serial No _____, filed _____

(3) ☐ U S Patent No _____ issued _____

is entitled to the benefits of "small entity" status for paying reduced fees under 35 USC 41(a) and (b) to the Patent and Trademark Office by virtue of the following:

(4) ☐ Each undersigned declares that he/she qualifies as an independent inventor, or would qualify had he/she made the invention, as defined in 37 CFR 1.9(c).

(5) ☐ The undersigned declares that he/she is an official empowered to act on behalf of the concern identified below; that this concern qualifies as a small business concern as defined in 37 CFR 1 9(d); that exclusive rights to the invention have been conveyed to and remain with the small business concern, or if the rights are not exclusive, that all other rights belong to small entities as defined in 37 CFR 1 9

(6) ☒The undersigned declares that he/she is an official empowered to act on behalf of the organization identified below, that this organization qualifies as a nonprofit organization as defined in

(a) ☒ 37 CFR 1 9(e)(1)

(b) ☐ 37 CFR 1.9(e)(2)

(c) ☐ 37 CFR 1 9(e)(3)

(d) ☐ 37 CFR 1 9(e)(4) State law of _____ that exclusive rights to the invention have been conveyed to and remain with the organization, or if the rights are not exclusive, that all other rights belong to organizations as defined in 37 CFR 1 9.

(7) Each person, concern or organization to which I/we have assigned, granted, conveyed or licensed, or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

(a) ☒ no such person, concern or organization

(b) ☐ persons, concerns or organizations listed below
[a separate declaration is required from each named person, concern or organization having rights to this invention averring to their status as "small entities."]

Full Name UNIVERSITE DE LIEGE

Address QUAI VAN BENEDEN 25, 4020 LIEGE -BELGIUM-

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

I/we acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement of small entity prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I/we hereby declare that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed

(8) JACQUES DELARGE — Typed Name of Inventor — Signature — Date

JEAN-MICHEL DOGNE — Typed Name of Inventor — Signature — Date June 2001

BERNARD MASEREEL — Typed Name of Inventor — Signature — Date July 25 2001

Typed Name of Inventor — Signature — Date

Typed Name of Inventor — Signature — Date

(9) UNIVERSITY OF LIEGE
Name of Small Business Concern or Nonprofit Organization

Dr NICOLE ANTHEUNIS — Typed Name — Signature — Date July 30, 2001

Responsable Brevets
Title of Signatory

DECLARATION AND POWER OF ATTORNEY U.S.A.

FOR ATTORNEYS' USE ONLY

ATTORNEYS' DOCKET NO.

ALL PATENTS, INCLUDING DESIGN

FOR APPLICATION BASED ON PCT, PARIS CONVENTION;

NON PRIORITY; OR PROVISIONAL APPLICATIONS

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or a first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

101 102

BENZENE-SULPHONAMIDE DERIVATIVES AND THEIR USES.

which is described and claimed in: ☐ PCT International Application No. _____ filed _____

☐ the attached specification ☐ the specification in application Serial No. _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specifications, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

103 104

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
9900026	EUROPEAN APPLICATION	15/01/1999	☒	☐
PCT/EP00/00225	INTERNATIONAL Application	12/01/2001	☐	☐
			☐	☐

I hereby claim the benefit under Title 35, United States Cod, §119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

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I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769), MARVIN R. STERN (20,640); MICHAEL R. SLOBASKY (26,421); JONATHAN H. SCHERER (29, 851); STANFORD W. BERMAN (17,909); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409).

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SEND CORRESPONDENCE TO:

JACOBSON, PRICE, HOLMAN & STERN
PROFESSIONAL LIMITED LIABILITY COMPANY
400 Seventh Street, N.W.
Washington, D.C. 20004

DIRECT TELEPHONE CALLS TO: *(please use Attorney's Docket No.)* (202) 638-6666

JACOBSON, PRICE, HOLMAN & STERN
PROFESSIONAL LIMITED LIABILITY COMPANY

Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME* OF INVENTOR	FAMILY NAME: DELARGE	GIVEN NAME: JACQUES	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: SPRIMONT BEV	STATE OR FOREIGN COUNTRY: BELGIUM	COUNTRY OF CITIZENSHIP: BELGIUM	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: HEID DES CHENES 7	CITY: SPRIMONT	STATE OR COUNTRY: BELGIUM	ZIP CODE: B-4140
202	FULL NAME* OF INVENTOR	FAMILY NAME: DOGNE	GIVEN NAME: JEAN-MICHEL	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: GRIVEGNEE BEV	STATE OR FOREIGN COUNTRY: BELGIUM	COUNTRY OF CITIZENSHIP: BELGIUM	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: AV. GRANDE ROTISSE 73	CITY: GRIVEGNEE	STATE OR COUNTRY: BELGIUM	ZIP CODE: B-4030
203	FULL NAME* OF INVENTOR	FAMILY NAME: MASEREEL	GIVEN NAME: BERNARD	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: FIZE-FONTAINE BEV	STATE OR FOREIGN COUNTRY: BELGIUM	COUNTRY OF CITIZENSHIP: BELGIUM	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: RUE CHALAIS 2	CITY: FIZE-FONTAINE	STATE OR COUNTRY: BELGIUM	ZIP CODE: B-4530

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE: July 17 2001	DATE: June 2001	DATE: July 25 2001

☐ Additional inventors are named on separately numbered sheets attached hereto.